multi-prodrug complex and at least two synthetic receptors, at least one of which is selected from the group consisting of drug receptors, transmitter receptors, autocoid receptors, cytokine receptors, antibodies, antibody fragments, molecular recognition units, engineered antibodies, antibody mimics, adhesion molecules, agglutinins, integrins, selectins, nucleic acids and biopolymers comprising nucleotides, saccharides, fatty acids, phenols, phosphates, sulfates, other organic monomers or nonbiologic monomers, wherein said synthetic receptors are selected by at least one of combinatorial selection, screening and selection of antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution, and wherein said selected drugs bind to the selected synthetic receptors with lower affinity than to the drugs' pathophysiologic receptors;

(b) binding the selected drugs to the selected synthetic receptors to produce a multi-prodrug complex; and

(c) administering the multi-prodrug complex to an organism so that the selected drugs dissociate from the synthetic receptors and bind to the drug's pathophysiologic receptors.

REMARKS

Claims 13-29 are pending in the instant application. Claims 13-29 stand rejected. Claims 13, 14, 16, 18, 20, 22, 24, 26 and 28 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

The Amendments

Claim 13 is amended to make clear that the selected synthetic receptor or selected drug comprising an immobilized prodrug complex is immobilized to a biologic or biocompatible structure by reciting "a biologic or biocompatible structure to which the selected synthetic receptor or selected drug is immobilized." "Immobilized" is a term of art meaning insolubilized by attachment to an insoluble matrix or solid support, as evidenced by excerpts from advertisements and articles enclosed herewith. Accordingly, a biologic or biological structure comprising an immobilized prodrug complex is, by definition, an insoluble matrix or solid support. Support for this amendment is found throughout the specification, particularly on page 11, line 28, bridging to page 12, line 4, and exemplified in Examples 3 and 4.

Claims 14 and 18 are amended to make clear that synthetic receptors of the instant invention are selected for the ability to bind drugs by reciting "synthetic receptor selected to bind said drug," as distinct from targeting antibodies disclosed in the cited prior art reference. Support for this amendment can be found throughout the specification, particularly in the abstract and on page 8, lines 25-28.

Claims 16, 20, 22, 24, 26 and 28 are amended to particularly point out the method by which synthetic receptors of the subject prodrug complexes are selected to bind drugs by reciting "selected by at least one of combinatorial selection, screening and selection of antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution." This amendment is

supported throughout the specification, particularly on page 10, lines 4-16, and exemplified in Examples 1 and 2.

The subject matter of the amended claims being fully supported in the subject application, Applicant respectfully requests that this amendment be entered into the application.

Rejection under 35 U.S.C. § 102

Claims 13-29 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Morgan, Jr. et al. (U.S. 5,106,951; hereafter '951). The Examiner suggests that '951 discloses drug/carrier complexes and a method of administering a drug via a drug/carrier complex where a drug binds to a polymeric carrier to form a prodrug complex that is capable of allowing drug dissociation from the polymeric carrier such that the drug retains its ability to bind to a site on or within a target cell. The Examiner also suggests that the '951 statement that the drug-conjugate is not exposed to derivatization conditions that might compromise the potency of the drug teaches that the drug is immobilized. The Examiner has acknowledged that the methods to identify the subject synthetic receptor are patentably distinct. However, it is suggested that the antibodies of '951 would be readily identifiable by the instant methods. Applicant respectfully traverses this rejection.

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Claim 13 recites "an immobilized prodrug complex." '951 does not teach or suggest an immobilized prodrug complex. Applicant respectfully disagrees with the Examiner's suggestion that the statement in '951 at column 4, lines 43-50 "does not expose the

drugs to harsh derivatization conditions and thereby does not compromise the potency of the drug" teaches that the drug is immobilized. The term "immobilized" is a term of art that means insolubilized by attachment to an insoluble matrix or solid support, as indicated by advertising and literature excerpts enclosed herewith. '951 actually teaches away from insolubilized conjugates by providing guidance to ensure that conjugates remain soluble (see, for example, column 3, lines 11-12; column 5, lines 18-19; column 9, lines 17-19; column 10, lines 55-62; column 14, lines 31-35; and column 15, lines 19-21).

In an earnest effort to advance the prosecution of this case, Applicant has amended claim 13 to recite "a biologic or biocompatible structure to which the selected synthetic receptor or selected drug is immobilized" to make clear that the prodrug complex is immobilized to the biologic or biocompatible structure. This amendment is supported throughout the specification, particularly on page 11, line 28, bridging to page 12, line 4, and exemplified in Examples 3 and 4. Immobilized compositions of the instant invention include prodrug complexes immobilized, for example, to biocompatible matrices, microparticles, liposomes, membranes, cells and implants, as disclosed throughout the specification, particularly on page 12, lines 5-10; page 13, lines 26-29; page 14, lines 11-22, page 19, lines 7-24; and page 20, line 27, bridging to page 21, line 15.

Claims 14 and 18 recite synthetic receptors identified by "a method selected from the group consisting of combinatorial selection, monoclonal antibody selection and antibody

engineering." These synthetic receptors are drug-binding molecules and therefore do not read on the antibodies of '951, which are not drug-binding molecules. Instead, the antibodies of '951 are targeting proteins that bind to target cells. See, for example, column 7, lines 10-18; column 4, lines 61-63; column 4, line 67, bridging to column 5, line 2; column 5, lines 47-48; column 7, lines 9-18; column 7, lines 48-50. To make clear that the selected synthetic receptors of the instant invention do not read on the antibodies of '951, Applicant has amended claims 14 and 18 to recite that the synthetic receptor is "selected to bind said drug."

The method of identifying synthetic receptors recited in claims 14 and 18 does not read on the '951 method of identifying a drug-binding molecule (i.e., "csDBM"), as the csDBM of '951 is designed to have functionalities that are opposite and complementary in structure to a drug molecule (column 5, line 63, bridging to column 6, line 6; column 8, lines 31-48; column 10, line 67, bridging to column 11, line 1). The csDBM of '951 can be found in nature and modified as necessary or specifically designed (column 1, lines 17-23; column 5, lines 2-4). '951 does not teach or suggest identifying a csDBM by antibody selection or antibody engineering. Further, the instant method of selecting synthetic receptors that bind to drugs for use in prodrug complexes is novel and distinct over the structure-based design method of '951, which requires detailed knowledge of the drug's structure. Unlike the method of '951, the instant invention is well-suited for delivery of large, complex drugs and structurally uncharacterized drugs.

Use of the subject synthetic receptors in prodrug complexes for delivery of emerging biopharmaceuticals such as proteins, peptides and oligonucleotides is supported throughout the specification, particularly on page 2, lines 7-16; page 5, lines 15-19; page 11, lines 16-27, and exemplified in Examples 2-4.

Claims 16 and 20 have been amended to clearly describe the synthetic receptor selection method of step b) in an active, definite fashion by reciting that the synthetic receptor is "selected by at least one of combinatorial selection, screening and selection of antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution." This amendment is supported throughout the specification, especially on page 10, lines 4-16, and exemplified in Examples 1 and 2. '951 does not teach or suggest methods for selecting a synthetic receptor for drug-binding properties by combinatorial selection, screening and selection of antibody, oligonucleotide or oligosaccharide libraries, or in vitro evolution.

Claims 22, 24, 26 and 28 have been amended to make clear that the claimed compositions and methods of enhancing drug delivery are limited to a specified method of selecting synthetic receptors by reciting synthetic receptors "selected by at least one of combinatorial selection, screening and selection of antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution." The method of selecting synthetic receptors recited in these claims is thus made identical to the amended language of claims 16 and 20, drawn to methods of making prodrug complexes. Support for these amendments can be found throughout

the specification, especially on page 10, lines 4-16, and in Examples 1 and 2. These claims as now amended are not anticipated by '951, as the method of selecting synthetic receptors used to make the instant prodrug complexes is not taught or suggested by '951.

In view of these amendments, Applicant submits that claims 13-29 are clearly distinguished from '951. Therefore, Applicant respectfully requests that the rejection of these claims under 35 U.S.C. § 102 be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 13-29 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Morgan, Jr. et al (5,106,951; hereafter '951). The Examiner has acknowledged that the methods used to identify the subject synthetic receptor are patentably distinct, but suggests that the antibodies of '951 would be readily identifiable by the instant methods. The Examiner has also acknowledged that '951 does not anticipate a multi-prodrug complex wherein the drugs are different, but argues that this composition would have been obvious to one skilled in the art at the time of the invention. This rejection is respectfully traversed.

Claim 13 as amended recites "an immobilized prodrug complex" and "a biologic or biocompatible structure to which the selected synthetic receptor or selected drug is immobilized." As discussed in connection with the rejection under 35 U.S.C. § 102, '951 does not teach an immobilized drug-binding conjugate and actually teaches away from insolubilized conjugates (column 3, lines 11-12;

column 5, lines 18-19; column 9, lines 17-19; column 10, lines 55-62; column 14, lines 31-35; and column 15, lines 19-21).

Claims 14 and 18 have been amended to recite synthetic receptors identified by "a method selected from the group consisting of combinatorial selection, monoclonal antibody selection and antibody engineering." '951 does not teach combinatorial selection, antibody selection or antibody engineering methods for selecting drug-binding molecules. In fact, '951 teaches away from the these selection methods by teaching that a drug-binding molecule is specifically designed or modified to fit the drug (abstract; column 1, lines 17-23; column 5, lines 2-4; column 5, line 63, bridging to column 6, line 6; column 8, lines 31-48). In the case of an oligopeptide drug-binding molecule, for example, the type and position of side chains in the oligopeptide are chosen according to the structure of the drug (column 10, line 63, bridging to column 11, line 1).

In contrast to the method of '951, selection of the instant synthetic receptors for drug-binding properties by combinatorial and antibody selection methods does not require detailed knowledge of a drug's structure or the steric location of functional groups on drug-binding molecules. This distinction over the method of '951 is important, for example, in developing delivery systems for structurally complex macromolecular drugs or drug leads, e.g., biopharmaceuticals. The utility of the instant methods and compositions for efficient delivery of emerging biopharmaceuticals such as proteins, peptides and oligonucleotides is supported throughout the specification, particularly on page 2, lines 7-16;

page 5, lines 15-19; page 11, lines 16-27, and exemplified in Examples 2-4. '951 does not teach or suggest a drug conjugate preparation or method that does not rely on detailed knowledge of the structure of the drug for structure-based design of a suitable csDBM. Nor does '951 teach or suggest practical methods for delivering complex macromolecular drugs, e.g., biopharmaceutical proteins, as enabled by synthetic receptor selection methods of the instant invention.

Claims 16, 20, 22, 24, 26 and 28 have been amended to recite a synthetic receptor "selected by at least one of combinatorial selection, screening and selection of antibodies, engineered antibodies, oligonucleotides or oligosaccharides, or in vitro evolution." '951 does not teach or suggest methods for selecting a synthetic receptor to bind to a drug by these molecular diversity-based methods. In fact, '951 teaches away from these synthetic receptor selection methods in disclosing that the drug-binding molecule is <u>designed to fit the drug</u> (abstract; column 5, line 63, bridging to column 6, line 6; column 8, lines 31-48) and is either <u>found in nature and modified</u> or <u>specifically designed</u> (column 1, lines 17-23; column 5, lines 2-4).

Applicant submits that the amended claims are clearly distinguished from the cited reference. '951 teaches away from the immobilized prodrug complex of claim 13 and neither teaches nor suggests the methods recited in each of claims 14-29 for selecting synthetic receptors that bind to drugs. Thus, the claimed invention would not have been obvious in view of the prior art. Withdrawal of this rejection is therefore respectfully requested.

CONCLUSION

Applicant submits that the foregoing comprises a full and complete response to the Office Action of record and that the present claims are clearly distinguished over the prior art. Applicant respectfully requests allowance of these claims.

Respectfully submitted,

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